Review

Hypothalamic and Limbic System Changes in Huntington's Disease

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Abstract. Huntington's disease (HD) is a neurodegenerative disorder caused by an expanded CAG repeat in the *huntingtin* gene. Today, the clinical diagnosis of the disease requires unequivocal signs of typical motor disturbances, which is thought to be due to pathology in the striatum of the basal ganglia. Increasing numbers of studies have emphasized that also non-motor symptoms and signs are common and occur early in HD. These include psychiatric disturbances and cognitive impairment as well as sleep disturbances with disrupted circadian rhythm, autonomic dysfunction and metabolic changes. Several of the non-motor features may be results of dysfunction of the hypothalamus and the limbic system, which are interconnected structures central in the regulation of emotion, sleep and metabolism. In fact, recent studies using postmortem tissue, magnetic resonance imaging and positron emission tomography have shown that hypothalamic and limbic system changes occur early in clinical HD. This review summarizes the current state of knowledge in this area based on clinical studies as well as experiments in animal models of the disease and establishes that hypothalamic and limbic system changes are part of the HD pathology.

Keywords: Huntingtin, huntington, hypothalamus, orexin, oxytocin, amygdala

HUNTINGTON'S DISEASE

Huntington disease (HD) is a monogenetic neurodegenerative disorder caused by an expanded CAG repeat in the HD gene, which codes for an expanded polyglutamine in the huntingtin (htt) protein [1]. Both the normal and mutant form of htt is expressed in all tissues in the body. It is a multi-functional protein regulating a number of key cellular functions such as vesicle transport and gene transcription [2, 3]. Loss of medium spiny GABA-ergic neurons in the striatum of the basal ganglia is a hallmark of HD and the staging of neuropathology is based on the extent of these changes [4]. Loss of neurons and general atrophy occur also in the cerebral cortex [5–7]. Neuronal intranuclear inclusions (NIIs) of aggregated mutant htt

are present in these regions [8]. Clinical diagnosis of HD currently requires unequivocally signs of motor disturbances such as chorea, which usually occur in midlife [9, 10]. These symptoms of HD are associated with the basal ganglia pathology. Death occurs 15–25 years after motor onset as no cure nor disease modifying treatment is available today [11, 12].

Individuals affected by the disease also suffer from psychiatric symptoms and cognitive decline [9, 10, 12, 13]. The psychiatric symptoms include depression, anxiety and irritability [14–16]. Reduced recognition of facial expression of emotions has consistently been reported [17–26]. Other emotional and cognitive changes include "frontal behaviour" characterized by apathy, disinhibition, and executive dysfunction [27, 28]. Psychiatric and cognitive changes are now known to precede the motor symptoms by many years [29]. Despite this, the focus on the movement disorder in the clinical practice and research of HD has been strong. Recent studies have revealed that also

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other non-motor symptoms and signs in HD occur early in the disease process. Sleep disturbances have a prevalence of around 90% and are characterized by an increased sleep onset latency, reduced sleep efficiency, frequent nocturnal awakenings, and delayed and shorted rapid eye movements [30–33]. Alterations of the circadian rhythm and autonomic dysfunction have been reported [34–37]. Disruption of body temperature homeostasis has been reported in several HD animal models [38, 39]. Furthermore, there are metabolic changes characterized by increased appetite, increased metabolism and weight loss in advanced stages of the disease [40–42]. Hence, the clinical presentation of HD is manifested by a spectrum of non-motor features that often precede the progressive motor dysfunction.

The limbic system is a group of anatomically and functionally interconnected nuclei in the brain that regulate emotion, sleep, circadian rhythm, temperature and body weight, functions disrupted in HD. The concept of the limbic system has evolved over time. Broca referred to the limbic lobe as part of the cerebral cortex that forms a rim around the corpus callous and the diencephalon on the medial side of the hemispheres (limbus is rim in latin), including structures such as the cingulate cortex, the parahippocampal gyrus and the hippocampus [43]. In 1937, Papez postulated that the cortical control of emotion involved the limbic lobe, and proposed a pathway from the posterior hypothalamus (mammillary bodies) through the anterior nucleus of the dorsal thalamus, the cingulate cortex, the hippocampus and then back to the hypothalamus via fornix, called the Papez circuit [44]. In parallel, the pioneering functional studies by Kluver and Bucy demonstrated the association between the limbic lobe and emotional and motivational processes in the primate brain [45]. Further work by MacLean [46] and Nauta [47] emphasized the critical connections between cortical structures and the hypothalamus as well as the midbrain in the limbic system. Today, the definition of the limbic system usually includes the following structures: the hippocampus, the gyrus cinguli, prefrontal cortex, the insula, septal nuclei, the amygdala, the hypothalamus, the ventral striatum, ventral tegmental area and the raphe nucleus [48, 49]. The increased awareness of the non-motor aspects of HD is now stimulating research investigating to what extent this system is affected in HD. This review summarizes the current state of knowledge in this area with special focus on the hypothalamus and highlights the major findings made so far in this growing and very exciting area of the HD field.

NEUROPATHOLOGY IN THE HD HYPOTHALAMUS

The hypothalamus consists of a number of nuclei that express a variety of hormones and neuropeptides involved in the control of the endocrine system as well as in the regulation of emotion, metabolism and sleep [50–55]. These nuclei include the paraventricular nucleus (PVN), the supraoptic nucleus, the suprachiasmatic nucleus (SCN), the arcuate nucleus, the nucleus tuberalis lateralis (NTL), the mammillary bodies and the lateral hypothalamic area. Investigations of pathological changes in the hypothalamus and the neuroendocrine system in HD began over 60 years ago. The results so far in both clinical HD and in different animal models of the disease have been discussed in detail in a few reviews published over the last couple of years [56–59]. The major positive results from studies investigating changes in the hypothalamus in clinical HD are illustrated in Fig. 1 and are discussed below.

Only few studies have investigated the neuropathology in the hypothalamus in HD. The first systematic analysis of a hypothalamic nucleus in HD was performed by Kremer et al. who described a reduction in the number of somatostatin neurons in and atrophy of the NTL [60–62]. The function of this specific nucleus is still unknown. Loss of the neuropeptide orexin (also called hypocretin), implicated in the sleep disorder narcolepsy as well as in the control of emotion and glucose metabolism, was then demonstrated in the lateral hypothalamus of HD brains with Vonsattel grades 1–4 [4, 63–65]. Although loss of around 30% of orexin-expressing neurons in HD was not sufficient to be reflected in the cerebrospinal fluid (CSF), this finding inspired further studies focusing on sleep in HD as well as on the extent of neuropathological changes in the hypothalamus [66–69]. Advances in the knowledge of hypothalamic changes in HD has however been limited by scarcity of tissue from this region in brain banks as well as due to lack of a clear morphological definition of the borders of this region and its nuclei. We have recently established a method to delineate this region using robust anatomical landmarks in formalin fixed brain sections stained with the cell marker cresyl violet and the myelin stain luxol fast blue [65]. Although our systematic stereological analyses of the whole hypothalamic region using this technique only detected a trend towards atrophy in a relatively small cohort of 9 HD cases from Vonsattel grade 1–4 compared to 8 controls, analyses of specific nuclei such as the PVN revealed a significant loss of neurons in
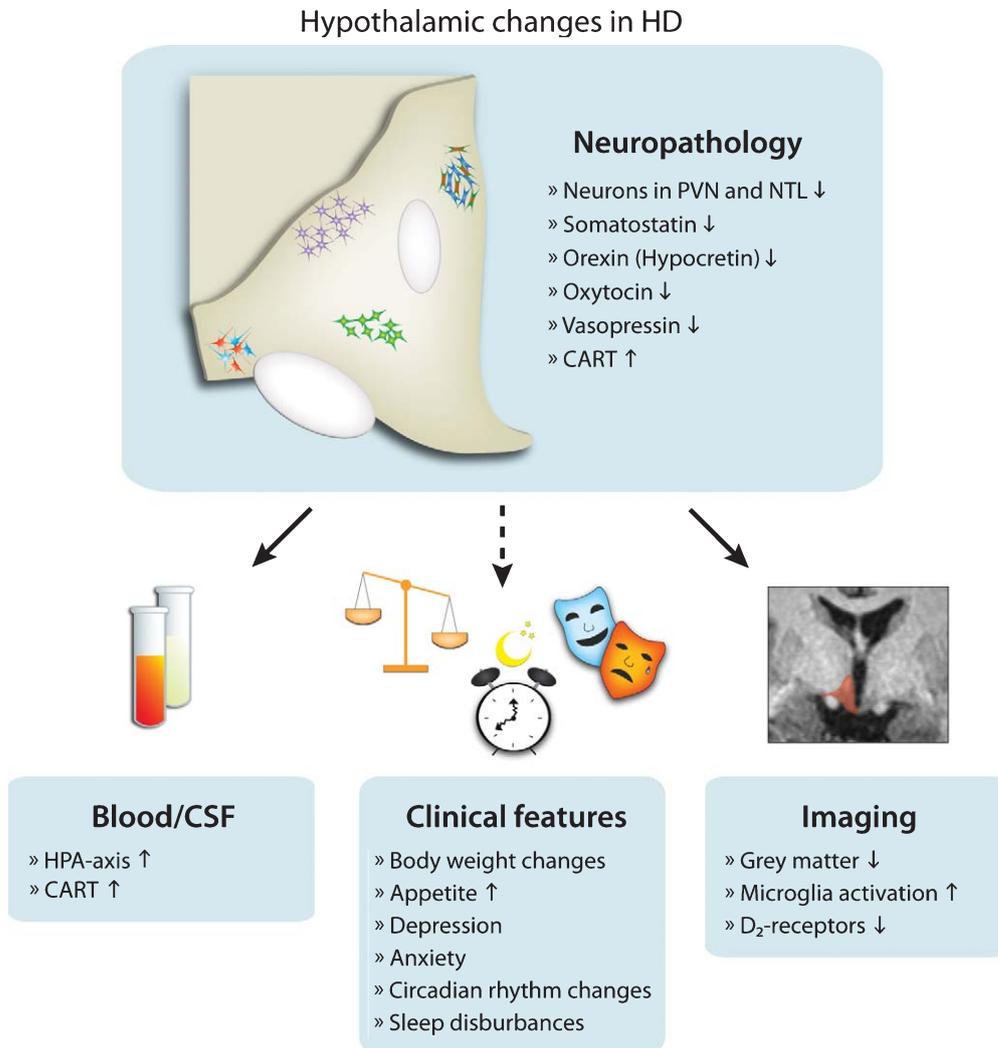
Hypothalamic changes in HD

Neuropathology

» Neurons in PVN and NTL ↓
» Somatostatin ↓
» Orexin (Hypocretin) ↓
» Oxytocin ↓
» Vasopressin ↓
» CART ↑

Blood/CSF

» HPA-axis ↑
» CART ↑

Clinical features

» Body weight changes
» Appetite ↑
» Depression
» Anxiety
» Circadian rhythm changes
» Sleep disburbances

Imaging

» Grey matter ↓
» Microglia activation ↑
» D_2-receptors ↓

Fig. 1. Hypothalamic changes in HD. The illustration summarizes the main positive results from studies investigating hypothalamic changes in clinical HD. CART: cocaine and amphetamine regulated transcript; CSF: cerebrospinal fluid; D2: dopamine D2; HPA: hypothalamic pituitary adrenal axis; NTL: nucleus tuberalis lateralis; PVN: paraventricular nucleus.

HD cases [65]. We also detected loss of oxytocin and vasopressin in the HD hypothalamus, which has also been found in several mouse models of HD [70–74]. Importantly, these neuropeptides have been implicated in social behavior and are now intensively studied as promising targets new therapies for a number of mental disorders [51, 75]. In particular, oxytocin has been found to increase trust, empathy and interpretation of emotional expression [51, 76, 77]. It is therefore possible that loss of oxytocin could be involved in causing some of the psychiatric aspects of HD including the reduced recognition of facial expression of emotions.

The neuronal cell population expressing cocaine and amphetamine regulated transcript (CART) has been found to be increased in the hypothalamic region, which is also reflected in the CSF [65, 78]. The neuropeptide CART is known to increase anxiety-like behaviour in rodents and has been implicated in mood disorders, and hence may therefore play a role in causing anxiety in HD [79–81]. However, not all neuropeptide- expressing populations in the hypothalamus are affected in HD. Neuronal populations expressing neuropeptide Y, histamine and melanin concentrating hormone were not altered in the HD hypothalamus of Vonsattel grades 1–4 [63, 65, 82]. Taken together, the neuropathological studies to date demonstrate that there is neuronal loss in specific nuclei of the HD hypothalamus as well as

specific alterations of metabolism and emotion controlling neuropeptides.

The molecular mechanism/s linking expression of mutant htt with hypothalamic pathology is still elusive. One potential link may be provided by huntingtin-associated protein-1 (HAP-1), a protein highly enriched in neurons in the hypothalamus which binds mutant htt stronger than wild-type htt [83]. HAP-1 is an important regulator of early post-natal feeding [84, 85] and expression of HAP-1 is reduced in transgenic HD mice that display weight loss [86]. However, the food intake controlling function of HAP-1 might not be important in adult stage [87] and other mouse models such as the BACHD mouse does not show altered expression levels at the time of metabolic disruption [70]. Another potential molecular mechanism underlying the hypothalamic dysfunction in HD may be transcriptional dysregulation as mutant htt has been found to suppress Brn2, a key transcription factor for the PVN neuropeptides [74].

HYPOTHALAMIC-RELATED NEUROENDOCRINE CHANGES IN HD

Although hypothalamic changes can be reflected in altered levels of neuroendocrine factors in CSF and blood, the assessment of such effects are complicated by the influence of gender, age, the diurnal rhythm, satiety level, medication as well as variability of available assays. The interpretation of results from studies published so far focused on the neuroendocrine changes in CSF and blood in HD patients is therefore limited by a large variation between and within studies, hence rendering it difficult to draw solid conclusions from the data [56–59]. A few clinical studies investigating hypothalamus-derived neuroendocrine factors in HD have however revealed interesting results. Besides the before mentioned increased levels of CART in CSF, analyses of the hypothalamic pituitary adrenal (HPA) axis in blood and urine together with mRNA levels of corticotrophin releasing hormone in the hypothalamus have collectively pointed to an upregulation of this endocrine axis in HD [88–92]. An activated HPA axis has been one of the most studied neuroendocrine changes in clinical depression and may exert negative actions also on cognitive function and energy metabolism [93]. Moreover, a delayed onset of the diurnal rise of the hormone melatonin has been found in HD patients, suggesting dysfunction of the SCN [94]. Interestingly, treatment with melatonin has recently been shown to inhibit toxicity induced by mutant htt and to delay disease onset in the R6/2 HD mouse model [95].

Hypothalamic changes can also affect afferent signals from the periphery such as leptin, a satiety signal from adipose tissue, ghrelin, an appetite stimulator from the gastric mucosa, and insulin, an anabolic peptide secreted from the pancreas [96]. Indeed, insulin resistance has been found in early stages of HD [97]. Reduced leptin and increased ghrelin levels have been found in later stages of HD, possibly reflecting the catabolic stage commonly send in advanced HD [98]. Other studies have however failed to detect significant difference in leptin and ghrelin levels between HD patients and controls [99, 100]. Leptin levels have been measured in several animal models of HD and have been found to be both increased and reduced depending on the model used and sometimes the age of the animals. Rodent models expressing a fragment of the mutant HD gene show reduced leptin levels; the published literature have reports of R6/2 from 6 weeks of age [101], the N171-82Q at its symptomatic phase [102] and the tgHD rat at 12 months of age [103]. The full length BACHD mouse displays increased leptin levels from 4 months of age [70] and in the YAC128 mouse it has been reported at 12 months of age [104]. Interestingly, the 140 CAG knock-in mouse model shows increased levels at 7 months of age and then decreased leptin levels at 22 months of age [101]. The latter together with the notion that full length mutant htt models may represent an early phase of HD and the fragment mutant htt models mimic later stages, suggest a biphasic curve of leptin alterations possibly mediated by hypothalamic dysfunction [70].

IMAGING FINDINGS IN THE HD HYPOTHALAMUS

Significant differences have been detected in the gray matter contents in the hypothalamic region between HD patients with motor symptoms and age- and sex-matched controls using voxel based morphometry (VBM) in magnetic resonance images (MRI) [105, 106]. In a recent study, we continued to investigate the extent of changes in the hypothalamic region using MR images from the PREDICT-HD study. The PREDICT-HD study is an international multicenter observational study which has enrolled a large number of individuals who have tested positive for the mutant htt gene but who have not yet manifested with motor symptoms, i.e., prodromal HD [107]. We found that there was a significant reduction in the gray matter

signal in the hypothalamic region in prodromal HD that paralleled alterations in the striatum and insula over a decade before expected onset of motor symptoms using VBM of MR images obtained using 1.5 Tesla (T) [108]. Using a different approach based on mathematical modeling, gray matter content in the hypothalamic region alone was powerful enough to distinguish prodromal HD from controls. It was also possible to distinguish different groups of prodromal HD divided based on different expected time of motor onset using only data from the hypothalamic region, suggesting progressive changes. Furthermore, several studies using positron emission tomography (PET) have found reductions of dopamine D2 receptors as well as microglia activation in the hypothalamic region of prodromal HD [109, 110]. Taken together, these results demonstrate that the hypothalamic region is affected early on in HD.

OTHER LIMBIC SYSTEM CHANGES IN HD

Imaging studies have been instrumental in detecting a number of changes also in other parts of the limbic system besides the hypothalamus in clinical HD

Limbic system changes in HD

» Grey matter ↓
» Volume ↓
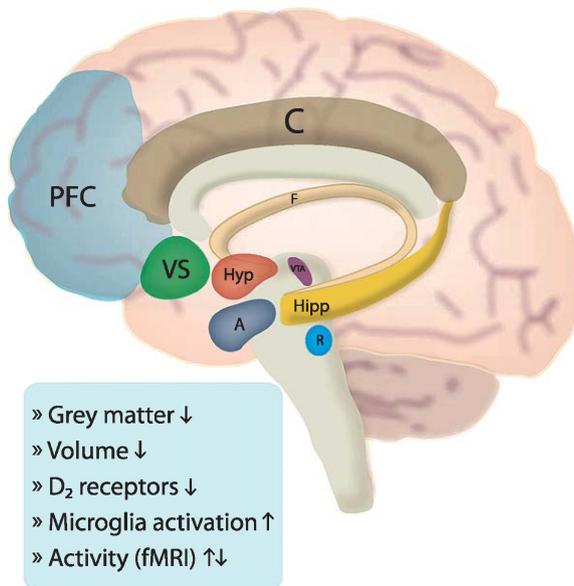» D$_2$ receptors ↓
» Microglia activation ↑
» Activity (fMRI) ↑↓

Fig. 2. Limbic system changes in HD. The illustration provides an overview of the main findings using imaging of the limbic system in clinical HD. A: amygdala; C: cingulate cortex; F: fornix; Hipp: hippocampus; Hyp: hypothalamus; PFC: prefrontal cortex; R: nucleus raphe; VS: ventral striatum; VTA: ventral tegmental area.

(Fig. 2). Grey matter loss and atrophy of the amygdala, the ventral striatum, the hippocampus, the insula, the anterior cingulate cortex and the prefrontal cortex have been reported [105, 110–117]. Reduction of D2 receptor binding has been detected in anterior cingulate cortex, insula and amygdala [110, 118]. Both increased and reduced activity in the anterior cingulate cortex has been found using different fMRI paradigms in prodromal and symptomatic HD as well as less functional connectivity with other cortical regions, indicating dysfunction of this area [119–123]. Reduced functional connectivity and decreased activation of the left lateral prefrontal cortex was found when verbal working memory was tested using fMRI in prodromal HD [124, 125]. Interestingly, an association between depressive state and hypoechogenicity in the raphe nucleus has been detected using transcranial sonography in HD patients, suggesting that serotonergic dysfunction in this nucleus may play a role in depression in HD [126]. Increased microglia activation is present in the amygdala already in prodromal HD, indicating early involvement of this area in the disease [110]. White matter degeneration has been detected in the fornix using diffusion tensor imaging [127]. Taken together, imaging studies show both dysfunction and signs of neurodegeneration early on in the limbic system in HD.

Neuropathological studies of the limbic structures in HD are rare. However, cell loss in the anterior cingulate cortex in HD cases with Vonsattel grades 1–3 has been reported to be associated with mood symptoms [128]. This area also contain ubiquitinated inclusions [129]. Neuropathological analysis of the prefrontal cortex in Vonsattel grade 3–4 HD brains has revealed neuronal loss and gliosis [130]. The synaptic protein complexin 2 has been found reduced already in grade 1 HD prefrontal cortex and glutamate uptake has been found decreased already in grade 0, again indicating early neuronal dysfunction in this area [131, 132]. Less neuronal density has been shown in the CA1 region of the hippocampus in HD [133]. A qualitative immunohistochemical study of the amygdala has shown severe atrophy [134] and biochemical studies have revealed increased levels of thyrotropin releasing hormone but normal levels of vasoactive intestinal peptide (VIP), somatostatin and neurotensin in the HD amygdala [135, 136]. Importantly, pathology in the amygdala could be involved in causing the reduced recognition of faces in HD [137]. Further systematic and detailed postmortem analyses of these structures as well as a continuation of imaging studies will be important to fully determine the extent and further characteristics of pathology in these limbic areas in HD.

Table 1
Summary of main alterations in the hypothalamic/limbic system in HD animal models

Region	Pathology	Model	References
Hypothalamus	Atrophy	R6/2 (12 w)	[72, 155, 156]
	Neuronal loss	R6/2 (12.5 w), N171-82Q (4 mo)	[64, 86]
	Loss of CART	R6/2 (12 w)	[72]
	Loss of CRH	R6/2 (8 w)	[72, 74, 89]
	Loss of GnRH	R6/2 (9 w)	[157]
	Loss of orexin	R6/2 (7.5 w), YAC128 (12 mo), AAV-hypo (4 w po)	[64, 67, 70]
	Loss of oxytocin	R6/2 (8 w), AAV-hypo (4 w po)	[70, 74]
	Loss of MCH	R6/2 (8 w)	[72]
	Loss of POMC	R6/2 (8 w)	[72]
	Loss of vasopressin	R6/2 (8 w), AAV-hypo (4 w po)	[70, 73, 74]
	Loss of VIP	R6/2 (11 w)	[158]
	Reduced HAP1 levels	N171-82Q (4 mo)	[86]
	Reduced clock genes	R6/2 (16 w)	[37]
	(mPer2, mBmal1)	R6/2 (16 w)	[37]
	Loss of Brn2	R6/2 (8 w)	[74]
	Upregulation of HPA axis	R6/2 (5.5 w)	[89]
Hippocampus	Reduced neurogenesis	R6/2 (3.5 w), R6/1 (20 w), N171-82Q (16 w), YAC128 (3 mo)	[140–143, 159]
	Increased ferritin	R6/2 (5–7 w)	[160]
	Reduced serotonin	R6/2 (4 w)	[161]
	Reduced HTR 1A, 2A, 1B	R6/1 (12 w)	[162]
	Reduced BDNF	R6/1 (12 w)	[163]
	Reduced PSA-NCAM	R6/1 (7 w), R6/2 (7 w)	[164]
Amygdala	Atrophy	TgHDrat (15 mo)	[165]
Cingulate cortex	Atrophy	R6/1 (9 mo)	[166]
Prefrontal cortex	Altered activity	R6/2 (7-8 w), TgHDrat (4-5 mo)	[167, 168]

The transgenic R6/2 and R6/1 mice express around 150 and 120 CAG repeats, respectively, in exon 1 of the human *HD* gene [148]. The N171-82Q transgenic mouse expresses the first 171 amino acids of human htt with 82 glutamines [169]. The YAC128 mouse expresses full length human mutant htt with 128 glutamines [170]. The transgenic HD rat (tgHDrat) has 51 CAG repeats in around the first 22% of the rat *HD* gene [171]. AAV-hypo is a mouse model constructed with selective hypothalamic injections of adeno-associated viral vectors expressing the first 853 amino acid fragment of human htt with 79 glutamines [70]. BDNF: brain-derived neurotrophic factor; CART: cocaine and amphetamine regulated transcript; CRH: corticotrophin releasing hormone; GnRH: Gonadotrophin releasing hormone; HPA: hypothalamic pituitary adrenal; HTR: serotonin (HT) receptor; MCH: melanin-concentrating hormone: POMC: proopiomelanocortin; PSA-NCAM: polysialylated form of the neural cell adhesion molecule; VIP: vasoactive intestinal peptide; po: post-injection.

INSIGHTS FROM ANIMAL STUDIES

Studies using animal models of HD have identified a number of different pathological changes in the hypothalamic/limbic system (Table 1). These studies have played an important role in stimulating further clinical investigations in this area. Also, functional studies of the orexin system and the SCN in the R6/2 mouse have shown that these systems can be pharmacologically modulated despite their pathological state, suggesting their therapeutic potential for treatment of non-motor features of HD [138, 139]. The extent of pathology in the animal models has however not always been reflected in clinical HD. As an example, numerous studies in transgenic HD mouse models have found decreased neurogenesis in the dentate gyrus of the hippocampus [140–143], which was later not found in human HD tissue [144]. This highlights the importance of validating findings made in animal models using clinical material. Animal models do provide useful tools to study causative relationships which can not be easily established in the clinical setting. One such tool is the BACHD mouse model which expresses full length mutant htt ubiquitously but is produced using a cre-loxP system rendering it possible to inactive mutant htt in specific brain regions or cells using cre-recombinase [145]. Several animal models of HD including the BACHD mouse model recapitulate the clinical features of increased appetite and insulin resistance [70, 89, 102, 146, 147]. Using adeno-associated viral (AAV) vector technology with cre-recombinase we recently showed that expression of mutant htt in the hypothalamus controls these aspects of the metabolic phenotype in the BACHD mouse [70]. Furthermore, selective expression of mutant htt in the hypothalamus of wild-type mice using AAV-vectors lead to the development of metabolic disturbances as well as reduced levels of oxytocin, vasopressin and orexin, features

found in both transgenic mouse models with ubiquitous expression of mutant htt as well as in clinical HD [70]. Hence, it is likely that hypothalamic dysfunction plays an important role in the development of metabolic changes in HD. However, one limitation of these experiments is the fact the full length BACHD mouse (and the YAC128 mouse) as well as the AAV-hypo model gain weight whereas the mutant htt fragment models lose weight similar to advanced stage HD patients [38, 70, 72, 86, 89, 104, 145, 148, 149]. Therefore, weight loss in HD may be related to pathology in other tissues of the body such as white and brown adipose tissue, the gastrointestinal system and/or the skeletal muscle [38, 101, 150–152]. Nevertheless, similar approaches based on the cre-loxP system and viral vector technology in animal models can be useful to determine the involvement of specific neuronal circuitries in the limbic system for the development of other non-motor features of the disease. Possibly the current therapeutic strategies to lower expression of htt should aim at targeting also these areas rather than only the typical chosen striatal region in order to have effects on non-motor aspects of HD.

CONCLUSION

HD has previously been viewed as a movement disorder with selective basal ganglia pathology. It is now clear that its clinical spectrum requires multidisciplinary care in the crossroads of neurology, psychiatry, genetics and cognitive medicine. Recent years' studies have highlighted that HD pathology also constitutes of hypothalamic dysfunction and changes in the limbic system, suggesting a neurobiological basis beyond the basal ganglia for the early non-motor features of the disease. As these alterations appear to occur early in the disease process, they may provide effective targets for disease-modifying interventions. However, further studies are needed to fully determine the role and extent of these changes in HD. Interestingly, as hypothalamic and limbic system changes are implicated also in mental illness and metabolic diseases, the intense efforts in research and drug development for these conditions may help to advance the understanding also of HD and provide new effective treatment options [75, 153, 154].

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